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Application Number

09/509,196

Filing Date

March 23, 2000

First Named Inventor

DALY, ROGER JOHN

Group Art Unit

1649

Examiner Name

CHERNYSHEV, OLGA N.

Attorney Docket Number

RICE-012

## ENCLOSURES (check all that apply)

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<input type="checkbox"/> After Final	<input type="checkbox"/> Petition	<input checked="" type="checkbox"/> Exhibit to Appellants' Brief: copy of Declaration of Dr. Yasumichi Hitoshi as originally filed on 2-10-03
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## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature

Date

June 28, 2006

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<b>APPELLANTS' BRIEF</b>  Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	RICE-012
	Confirmation No.	8868
	First Named Inventor	DALY, ROGER J.
	Application Number	09/509,196
	Filing Date	March 23, 2000
	Group Art Unit	1649
	Examiner Name	CHERNYSHEV, O.
Title: "A POTENTIAL EFFECTOR FOR THE GRB7 FAMILY OF SIGNALLING PROTEINS"		

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Final Rejection dated February 1, 2006. No claims have been allowed, and Claims 5-7, 19-22, 24-29, and 31-41 are pending. Claims 5-7, 19-22, 24-29, and 31-41 are appealed. A Notice of Appeal was filed on April 28, 2006.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815 to cover any fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815.

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**REAL PARTY IN INTEREST**

The inventors named on this patent application assigned their entire rights in the invention to Garvan Institute of Medical Research. The application is licensed to Rigel Pharmaceuticals.

**RELATED APPEALS AND INTERFERENCES**

There are no appeals pending which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

**STATUS OF CLAIMS**

The present application was filed on March 23, 2000 with Claims 1-15. During prosecution, Claim 16-41 were added and Claims 1-4, 8-18, 23, and 30 were cancelled. Accordingly, Claims 5-7, 19-22, 24-29, and 31-41 are pending in the present application, all of which claims are currently rejected and appealed herein.

**STATUS OF AMENDMENTS**

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

**SUMMARY OF CLAIMED SUBJECT MATTER**

The pending claims are drawn in pertinent part to an isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2, as well as vectors, transformed host cells, and methods of producing a protein by culturing such transformed host cells. The claimed polynucleotides include: isolated polynucleotides comprising a sequence as shown in SEQ ID NO:1, nucleotides 694-1614 of SEQ ID NO:1, or comprising a sequence having at least 95% sequence identity to SEQ ID NO:1; isolated polynucleotides comprising a sequence encoding an amino acid sequence of SEQ ID

NO:2, or amino acid residues 232-538 of SEQ ID NO:2; isolated polynucleotides comprising a sequence having at least 95% sequence identity to a sequence encoding amino acid residues 232-538 of SEQ ID NO:2; isolated polynucleotides comprising a sequence of nucleotides 694-1614 of SEQ ID NO:1; and isolated polynucleotides comprising a sequence encoding amino acid residues 232-888 of SEQ ID NO:2.

Below is a description of each appealed claim. Where support for each claim can be found in the specification is listed in parentheses, is given as exemplary, and is not intended to be exhaustive. Paragraph and page numbers used below are those appearing in the US Patent Application Publication No. 2002/0037582, published March 28, 2002, for the instant application.

Independent Claim 32 recites an isolated polynucleotide molecule having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2. (See the specification at paragraph [0007]).

Claim 5 depends from claim 32 and specifies a host cell transformed with the polynucleotide molecule of claim 32. (See the specification at paragraph [0010]).

Claim 6 depends from claim 5 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 7 depends from claim 5 and specifies a method of producing a protein, wherein the host cell of claim 5 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 19 depends from claim 32 and specifies that the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0007]).

Claim 20 depends from claim 32 and specifies a vector including a polynucleotide molecule according to claim 32. (See the specification at paragraph [0010]).

Claim 21 depends from claim 20 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Independent Claim 22 recites an isolated polynucleotide molecule including a nucleotide sequence having at least 95% sequence identity to that shown in SEQ ID NO:1. (See the specification at paragraph [0007]).

Claim 24 depends from claim 22 and specifies a host cell transformed with the polynucleotide molecule of claim 22. (See the specification at paragraph [0010]).

Claim 25 depends from claim 24 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 26 depends from claim 24 and specifies a method of producing a protein, wherein the host cell of claim 24 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 27 depends from claim 22 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Claim 28 depends from claim 22 and specifies a vector including a polynucleotide molecule according to claim 22. (See the specification at paragraph [0010]).

Claim 29 depends from claim 28 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Claim 31 depends from claim 32 and specifies that the polynucleotide molecule includes a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2. (See the specification at paragraph [0007]).

Independent claim 33 recites an isolated polynucleotide molecule including a nucleotide sequence having at least 95% sequence identity to a nucleotide

sequence encoding amino acid residues 232-538 of SEQ ID NO:2. (See the specification at paragraphs [0007] and [0049] and Figure 1).

Claim 34 depends from claim 33 and specifies a host cell transformed with the polynucleotide molecule of claim 33. (See the specification at paragraph [0010]).

Claim 35 depends from claim 34 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 36 depends from claim 34 and specifies a method of producing a polypeptide, wherein the host cell of claim 34 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 37 depends from claim 33 and specifies that the nucleotide sequence includes a nucleotide sequence of nucleotides 694-1614 of SEQ ID NO:1. (See the specification at paragraph [0049]).

Claim 38 depends from claim 37 and specifies a vector including a polynucleotide molecule according to claim 33. (See the specification at paragraph [0010]).

Claim 39 depends from claim 38 and specifies a vector including a polynucleotide molecule according to claim 38. (See the specification at paragraph [0010]).

Claim 40 depends from claim 33 and specifies the isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule includes a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2. (See the specification at paragraph [0049] and Figure 1).

Claim 41 depends from claim 33 and specifies the isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule includes a nucleotide sequence encoding amino acid residues 232-888 of SEQ ID NO:2. (See the specification at paragraph [0049] and Figure 1).

**GROUND OF REJECTION TO BE REVIEWED ON APPEAL**

Claims 5-7, 19-22, 24-29, and 31-41 stand rejected under 35 U.S.C. § 101 as allegedly being drawn to an invention with “no apparent or disclosed specific and substantial credible utility.” The quoted phraseology is that employed by the Examiner in the Final Office Action at paragraph 5.

Claims 5-7, 19-22, 24-29, and 31-41 stand further rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement (“how to use”) by virtue of the rejection under 35 U.S.C. § 101.

**ARGUMENTS**

I. In summary, the rejection under 35 U.S.C. § 101 is based on the Examiner’s allegation that the claimed invention has “no apparent or disclosed specific and substantial credible utility.” Appellants submit that this rejection is flawed both legally and procedurally, and request withdrawal of this rejection.

**Legal Flaws in the § 101 Rejection**

Appellants’ specification discloses at least two utilities for the claimed invention:

- 1) The claimed polynucleotides are useful in distinguishing cancer cells from normal cells because they are differentially expressed in certain human cancers, e.g., breast and prostate cancer; and
- 2) The claimed polynucleotides are useful for distinguishing cancer cells from normal cells because they encode a polypeptide (designated 2.2412) that binds to the signaling proteins Grb7 and to Grb14, each of which is known to be differentially expressed in certain cancer cells relative to normal cells. Therefore, because the 2.2412 polypeptide acts as “bait” for Grb7 and Grb14, it is useful as a tumor marker and/or as a prognostic indicator for these cancers.

With regard to the above utilities, Appellants have established in the file record that it was known in the art as of Appellants’ filing date that Grb7 and Grb14 are differentially expressed in cancer cells (breast, prostate, gastric, and esophageal cancer) compared to normal cells. Appellants have provided extrinsic evidence that



Grb7 and Grb14 were recognized as markers for cancer at the time of filing of the present application, as well as extrinsic and intrinsic evidence<sup>1</sup> that the 2.2412 polypeptide encoded by the claimed polynucleotide specifically binds to Grb7 and Grb14.

The Examiner dismissed the above evidence by virtue of her position that there is no factual evidence within the instant disclosure regarding differential expression of the polynucleotide encoding 2.2412. She appears to be requiring data showing altered levels or forms of a polynucleotide encoding 2.2412 polypeptide in diseased tissue versus corresponding healthy tissue. She criticized some data published before Appellants' filing date regarding differential expression as "inconclusive." She dismissed other articles published before Appellants' filing date relating to coexpression and coamplification of Grb7 in gastric and esophageal cancers because Appellants' specification does not disclose these types of cancer. She apparently has not considered evidence published after the filing date that supports Appellants' statements of utility.

The Examiner also appears to be confusing a statement of utility, which must be recited in the application as filed, with extrinsic evidence that supports such a statement. The latter evidence in support of a utility statement need not appear in the application as filed. Appellants have cited *In re Hogan*, 194 USPQ 527, 537 (CCPA 1977), which held that later publications that substantiate Applicant's assertions of utility or other art-related facts existing on the filing date are acceptable. The Examiner acknowledged this citation in the Final Office Action, but her only response to this and to all of Appellants' other arguments was a discussion of *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). Appellants will discuss *Fisher* below.

Appellants have disclosed<sup>2</sup> that the Grb7 family proteins exhibit differential expression in certain human cancers (particularly breast and prostate cancer) (emphasis added). The phrase *certain human cancers* is a generic statement that embraces the gastric and esophageal cancers disclosed by the Kishi *et al.* and Tanaka *et al.* articles, respectively, cited by Appellants in support of their utility

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<sup>1</sup> See the specification at, for example, pages 10-11.

<sup>2</sup> See the specification at, for example, page 5.

statement. Apparently the Examiner is requiring that a generic statement of utility be accompanied by an exhaustive litany of specific utilities that fall within the generic utility statement in order for earlier or later published specific knowledge to substantiate Appellants' assertion of utility. This is an unduly burdensome and improper standard.

Appellants submit that the standard used by the Examiner for satisfying the utility requirement is higher than that set forth in the § 101 Guidelines or Training Materials. To satisfy the utility requirement an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention. MPEP § 2107 II(B). Appellants have provided at least two assertions of utility in their specification (see above) that satisfy the utility requirement. If the asserted utility is credible and if it is more likely than not that a person of ordinary skill in the art would consider the asserted utility specific and substantial, the utility requirement is met. MPEP § 2107 II(C). This is a preponderance of the evidence standard, a relatively low standard, which is lower than a clear and convincing evidence standard, which itself is lower than a beyond a reasonable doubt standard.

In this regard, extrinsic evidence, especially published before Appellants' filing date, is also evidence of the level of skill in the art. Therefore, Appellants have properly relied upon such evidence to substantiate their utility statement. In addition, because of the evidentiary standard set forth in MPEP § 2107 II(C) (see above), such evidence should be considered by the Examiner in evaluating a utility statement as being credible or specific and substantial. However, the Examiner has dismissed the relevance of the cited extrinsic evidence because she appears to be confusing *assertion* of a utility statement after the filing date (improper) with *substantiation* of an existing utility statement by extrinsic evidence (proper) (see above).

Moreover, by requiring exhaustive data, the Examiner is asking the Appellants to prove their utility statement unequivocally. Thus, the Examiner is applying improperly a standard higher than a preponderance of the evidence standard. In addition, the Examiner has asserted "that the observed overexpression of Grb14 protein in a prostate or breast cell line cannot be unequivocally indicative of Grb14

being a marker for these types of cancer...." September 15, 2005 Office Action at pages 7-8 (emphasis added). This is further evidence that she is employing a standard higher than a preponderance of the evidence standard. Appellants are not required to prove their utility unequivocally.

The burden is on the Office to substantiate any reasons for doubting an asserted utility. Appellants ordinarily submit data only when a *prima facie* case of no specific and substantial utility or no credible utility has been established by the Office. The Examiner has cited only a general paper by Baguley *et al.*. In so doing, once again the Examiner has not met the evidentiary standard of a preponderance of the evidence. The Daly *et al.* paper (J. Biol. Chem. **1996**, 271:12502-12510) cited previously by Applicant is far more relevant to breast and prostate cancer than is the general Baguley *et al.* paper. Therefore, at best there is a 50-50 tie, pitting Appellants' word against the Examiner's. Because a *tie* does not meet the preponderance of the evidence standard, the tie should be broken in favor of Appellants and the rejection withdrawn, since the Examiner has not established a *prima facie* case for a rejection for lack of utility.

Nevertheless, Appellants have in fact submitted (on February 10, 2003) a Declaration under 37 CFR § 1.132 by Dr. Yasumichi Hitoshi containing additional data that confirms the use of the 2.2412 protein as a tumor marker. Dr. Hitoshi declared that at least two publications have associated 2.2412 expression with human cancers. Specifically, 2.2412 has been reported to be a tumor-specific antigen as evidenced by detection of 2.2412 antibodies in sera of breast cancer patients<sup>3</sup> and in sera of patients having meningioma.<sup>4</sup>

Furthermore, Dr. Hitoshi declared that it in his opinion a person having ordinary skill in the art reading the instant application at the time of the filing thereof would have found the assertion that 2.2412 is a tumor marker to be credible. In addition, Dr. Hitoshi declared further that the additional data submitted in the declaration further support the assertion in the instant application that the 2.2412 protein and its encoding polynucleotide are useful as a tumor marker.

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<sup>3</sup> Kuimov *et al.*, 2001 Genes Immun. 2:52-5.

<sup>4</sup> Monz *et al.*, 2001 Clin. Cancer Res. 7:113-9.

The Hitoshi declaration is further extrinsic evidence that substantiates Appellants' statement of utility. It is improper to dismiss summarily the contents of this declaration because they were not part of the specification as filed (see above).

After discussing *Fisher* in the Final Office Action, the Examiner made an unsupported statement that "detection of an isolated polynucleotide molecule of SEQ ID NO:1 or the encoded polypeptide of SEQ ID NO: 2 provides no information regarding presence or absence of any pathological condition, including breast or other form of cancer." First, such a statement does not break the 50-50 tie; it is but another example of the Examiner's unsupported opinion, which is contrary to the evidence of record. Second, the statement is not relevant to each of Appellants' utilities delineated above. Appellants reiterate that to satisfy the utility requirement an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention. MPEP § 2107.

Appellants submit that the *Fisher* case is one dealing with ESTs. The court in *Fisher* held that "the claimed ESTs are, in words of the Supreme Court, mere 'object[s] of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *Fisher* at 1373 (citation omitted). Unlike in *Fisher*, Appellants' utility statement is supported by evidence which would lead one of ordinary skill in the art to consider Appellants' utility statement credible as well as specific and substantial. However, to the extent that the *Fisher* court stated that the utility threshold is not high (both the applicant and the solicitor agreed to this), it is very much on point. *Fisher* at 1370.

Appellants respectfully request withdrawal of this rejection.

#### **Procedural Flaws in the § 101 Rejection**

The Examiner rejected the claims under 35 U.S.C. § 101 "because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility..." It is unclear from this statement whether the Examiner considers Appellants' utilities 1) credible but not specific and substantial or 2) specific and substantial but not credible. Appellants have requested clarification

from the Examiner, but have received none. Accordingly, the statement of the rejection remains unclear.

The phrasing of the rejection is contrary to the Utility Guidelines, contrary to the MPEP at § 2107 II(C), and even contrary to *In re Fisher, supra*, cited by the Examiner. In *Fisher*, the government contended “that a patent applicant need disclose only a single specific and substantial utility ... the very standard articulated in the PTO’s ‘Utility Examination Guidelines’ ... and followed here when examining the ... application.” *Fisher* at 1370. It should be noted that the court did not say single specific and substantial credible utility (i.e. the court did not employ the phraseology used by the Examiner in the instant Final Rejection). Based on the court’s language, it is apparent that the court and PTO considered *Fisher*’s utility credible, but not specific and substantial. However, the phrasing of the present rejection does not permit one to understand (as in *Fisher*) whether the Examiner considers the utility credible, but not specific and substantial because all three terms (*credible*, *specific*, and *substantial*) appear in the statement of the rejection. The Utility Guidelines provide for a rejection for no specific and substantial utility, and they provide for a rejection for no credible utility. The Guidelines do not provide for a rejection for no specific and substantial credible utility.

The Examiner cited MPEP § 2107 II(B) in response to Appellants request for clarification, but MPEP § 2107 II(C) would appear to control over MPEP § 2107 II(B), since MPEP § 2107 II(C) discusses how to make (phrase) the rejection. MPEP § 2107 II(C) provides for two rejection situations: (1) where the asserted utility is *not* specific or substantial, and (2) where the asserted utility *is* specific and substantial, but is not credible. In situation (1), the issue of credibility is not reached in the rejection. In situation (2), the only basis for rejection is lack of credibility. Therefore, MPEP § 2107 II(C) does not provide for a rejection under 35 U.S.C. § 101 for lacking an apparent or disclosed specific and substantial credible utility, i.e., it does not provide for the phraseology employed by the Examiner.

II. In summary, the enablement (“how to use”) rejection under 35 U.S.C. § 112, first paragraph is based on the Examiner’s allegation that one would not know

how to use the claimed invention because allegedly it is not supported by either a clear asserted utility or a well established utility for reasons set forth in the rejection under 35 U.S.C. § 101.

Appellants reiterate their arguments above. Because the § 101 rejection is flawed for the reasons set forth above, the enablement rejection must fall. Appellants respectfully request withdrawal of this rejection.

**SUMMARY**

Claims 5-7, 19-22, 24-29, and 31-41 are not unpatentable under 35 U.S.C. §§ 101 and 112, first paragraph. Appellants' specification discloses at least two utilities that are credible and more likely than not specific and substantial. Therefore, rejections for lack of utility and enablement are improper.

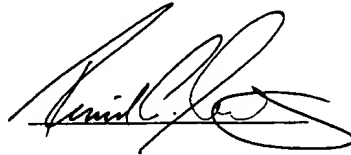
**RELIEF REQUESTED**

The Appellants respectfully request that the rejection of under 35 U.S.C. §§ 101 and 112, first paragraph be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: June 28, 2006

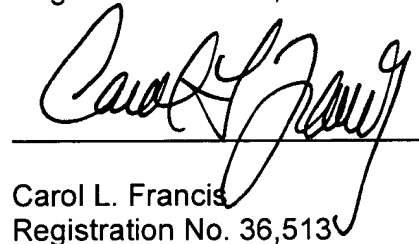
By:



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**Claims Appendix**

5. A host cell transformed with the polynucleotide molecule of claim 32.
6. The host cell of claim 5, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.
7. A method of producing a protein, comprising culturing the host cell of claim 5 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.
19. An isolated polynucleotide molecule according to claim 32, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.
20. A vector comprising a polynucleotide molecule according to claim 32.
21. A vector according to claim 20, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.
22. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to that shown in SEQ ID NO:1.
24. A host cell transformed with the polynucleotide molecule of claim 22.
25. The host cell of claim 24, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.
26. A method of producing a protein, comprising culturing the host cell of claim 24 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.



27. An isolated polynucleotide molecule according to claim 22, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.
28. A vector comprising a polynucleotide molecule according to claim 22.
29. A vector according to claim 28, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.
31. A polynucleotide according to claim 32, wherein the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2.
32. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2.
33. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2.
34. A host cell transformed with the polynucleotide molecule of claim 33.
35. The host cell of claim 34, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.
36. A method of producing a polypeptide, comprising culturing the host cell of claim 34 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.

37. An isolated polynucleotide molecule according to claim 33, wherein the nucleotide sequence comprises a nucleotides sequence of nucleotides 694-1614 of SEQ ID NO:1.
38. A vector comprising a polynucleotide molecule according to claim 33.
39. A vector according to claim 38, wherein the polynucleotide comprises a nucleotides sequence of nucleotides 694-1614 of SEQ ID NO:1.
40. The isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule comprises a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2.
41. The isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule comprises a nucleotide sequence encoding amino acid residues 232-888 of SEQ ID NO:2.

**EVIDENCE APPENDIX**

No evidence submitted under 37 CFR §§ 1.130 or 1.131 has been relied upon by Appellants in this Appeal. Appellants rely upon the Declaration of Dr. Yasumichi Hitoshi under 37 CFR §1.132, originally filed on February 10, 2003, a copy of which is attached hereto.

**RELATED PROCEEDINGS APPENDIX**

There are no decisions rendered by a court or the Board which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

Atty Dkt. No.: RICE012

USSN: 09/509,196

CERTIFICATE OF MAILING	
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<b>DECLARATION OF YASUMICHI HITOSHI UNDER 37 C.F.R. § 1.132</b>  Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	RICE-012 8868
	First Named Inventor	Roger John Daly
	Application Number	09/509,196
	Filing Date	March 23, 2000
	Group Art Unit	1646
	Examiner Name	Olga N. Chernyshev
	Title	"Potential Effector for the GRB7 Family of Signalling Proteins"

Dear Sir:

1. I, Yasumichi Hitoshi, M.D., Ph.D. declare and say I am a resident of the U.S.A. My residence address is 331 Callippe Court, Brisbane, CA 94005.

2. I hold a M.D. degree, which I received from Kumamoto University Medical School in 1987. I further hold a Ph.D. degree which I received from Kumamoto University Medical School in 1991. I am an expert in the fields of oncology research, retroviral technology, and cell cycle regulation. A copy of my curriculum vitae is attached as Exhibit 1.

3. I am currently hold the position of Associate Director at Rigel Pharmaceuticals, Inc.

4. I have read both the specification of U.S. patent application serial no. 09/509,196 (the '196 application) and the Office Action dated November 5, 2002 issued by the Examiner in this same patent application.

Atty Dkt. No.: RICE012  
USSN: 09/509,196

5. I understand that the pending claims are directed to a polynucleotide encoding the protein 2.2412, which is now referred to in the literature as Tankyrase2 or TaHo (Tankyrase Homolog), as well as vectors and host cells containing this polynucleotide, and use of this polynucleotide to produce the encoded 2.2412 protein.

6. I understand that the Patent Office has rejected all pending claims on the basis that the utility asserted in the '196 application is not credible. I further understand that the asserted utility disputed by the Patent Office is the use of 2.2412-encoding polynucleotide or 2.2412 protein as a tumor marker.

#### Review of the '196 Application

7. The '196 application sets out the following statements (page and line numbers in brackets refer to the specific parts of the '196 application::

- a) 2.2412 protein is an effector protein for the Grb7 family of signalling proteins (a protein that specifically binds to a signaling protein to facilitate a signal transduction cascade)
  - i) 2.2412 protein specifically binds Grb14 and specifically binds Grb7 (page 10, line 26 to page 11, line 32)
  - ii) binding of 2.2412 protein to Grb14 requires the N-terminal region of Grb14, which contains highly conserved proline-rich motif thought to mediate interaction of the Grb7 family of proteins with their effectors (page 11, lines 29-32)
  - iii) 2.2412 contains multiple ankyrin repeats, which are known to have a role in protein-protein interactions (page 9, lines 25-34)

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**b) Grb7 family members are signal transduction molecules that exhibit**

**differential expression in certain human cancers (particularly breast cancer) (page 5, lines 13-15). Specifically, at the time of filing**

- i) Grb7 family members were known to be associated with oesophageal carcinoma,<sup>1</sup> primary gastric cancer,<sup>2</sup> and breast cancer.<sup>3</sup>
- ii) Grb14 was known to be differentially expressed in breast cancer<sup>4</sup>
- iii) Grb7 was known to be differentially expressed in breast cancer<sup>5</sup>

8. Given that 2.2412 specifically binds Grb14 and specifically binds Grb7, each which were known at the time the application was filed (September 23, 1997) to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed (specification page 5, lines 13-16).

9. In my opinion, the '196 application sets out a credible association of 2.2412 expression and human cancers.

10. This association of 2.2412 expression with human cancers has been further supported in at least two publications. Specifically, 2.2412 (also known as Tankyrase2<sup>6</sup>) has been reported to be a tumor-specific antigen as evidenced by detection of anti-Tankyrase2 antibodies in sera of breast cancer patients<sup>7</sup> and in sera of patients having meningioma.<sup>8</sup>

<sup>1</sup> Tanaka et al. 1997 Cancer Res. 57:28-31.

<sup>2</sup> Kishi et al. 1997 Biochem Biophys. Res. Commun. 232:5-9.

<sup>3</sup> Stein et al. 1994 EMBO J 13:1331-40.

<sup>4</sup> Daly et al. 1996 J. Biol. Chem. 271:12502-10.

<sup>5</sup> Stein et al. 1994 EMBO J 13:1331-40

<sup>6</sup> Lyons et al. 2001 J. Biol. Chem. 276:17172-80.

<sup>7</sup> Kuminov et al., 2001 Genes Immun. 2:52-5.

<sup>8</sup> Monz et al., 2001 Clin. Cancer Res. 7:113-9.

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11. In summary, after reviewing the '196 application, it is my opinion that a person having ordinary skill reading the '196 application at the time the application was filed (September 23, 1997) would find the assertion that 2.2412 (Tankyrase2) is a tumor marker to be credible in view of the disclosure in the specification as set out above.

**Additional Data Confirming the Use of 2.2412 as a Tumor Marker**

12. In my position at Rigel Pharmaceuticals, Inc., I have directed others and personally performed research to examine the expression of 2.2412 (also referred to as Tankyrase2 or Tankyrase Homologue (TaHo)) in both normal and cancerous human cells.

13. Expression of 2.2412 was examined using a Taqman Assay. Matched tumor and normal cDNAs from lung and breast tissue were obtained from two different sources: BioChain Inc. and Clontech (clinical histories of Clontech cDNAs were not available). Location of the primers within the 2.2412 (TaHo) sequence are indicated as bolded and underlined sequences in Exhibit 2. In addition, the TaHo sequence was aligned with the Tankyrase sequence in order to demonstrate the specificity of the Taqman analysis using these primers for Tankyrase homologue. Analysis was done in triplicate and standard errors for normal and tumor tissue were determined. Expression levels in the matched samples were normalized to Ribosomal Protein S9 (S9) and the 23kD Highly Basic Protein (HBP).

14. The results of these studies are shown in Exhibit 3. As shown in the graphs, 2.2412 is expressed at significantly higher levels in two types of lung cancer (bronchioalveolar carcinoma and large cell carcinoma) relative to normal lung tissue. 2.2412 is also expressed at significantly higher levels in three types of breast cancer (invasive ductal carcinoma, intraductal carcinoma and invasive lobular carcinoma) compare to normal breast tissue.



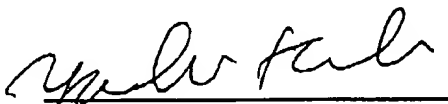
Atty Dkt. No.: RICE012

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15. These data further support the assertion in the '196 application that the 2.2412 protein and its encoding polynucleotide are useful as a tumor marker.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

2/3/03  
Date

  
Yasumichi Hitoshi, Ph.D.

## Attachments:

Exhibit 1: Curriculum vitae of Dr. Yasumichi Hitoshi

Exhibit 2: Primers used in expression analysis of 2.2412

Exhibit 3: Graphs showing expression of 2.2412 in normal and cancerous human cells

## EXHIBIT 1

### Curriculum vitae

**Name:** Yasumichi Hitoshi, MD. Ph.D.  
**Born:** November 21, 1961. Kumamoto, Japan  
**Citizenship:** Japan

**Present Position:** Associate director, Project leader  
**Present address:** Department of Cell Biology  
Rigel pharmaceutical Inc.,  
240 East grand avenue,  
CA 94081  
U.S. A.  
Telephone: 650-624-1128  
Facsimile: 650-624-1101  
E-mail: yhitoshi@rigel.com

#### Professional experience:

2002.7-present Associate director, Project leader  
Department of Department of Cell Biology,  
Rigel pharmaceutical Inc.

#### Research:

2002.1-2002.7 Group leader, Project leader  
Department of Department of Cell Biology,  
Rigel pharmaceutical Inc.

#### Research:

1998.12-2001.12 Senior scientist, Project leader  
Department of Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Identification of proteins and peptides that play an important role  
in cell cycle regulation of specific tumor cells using retroviral  
functional screens.

- 1998.2-1998.12 Senior scientist  
Department of Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Characterization of a membrane receptor, Toso, which inhibit  
TNF receptor family-induced apoptosis.
- 1995.3-1998.2 Postdoctoral Fellow  
Department of Molecular Pharmacology, Stanford University.  
Research: Analysis of signaling pathway using high titer retrovirus.  
Scientific Advisor: Assistant Professor Garry P. Nolan
- 1992.1-1995.3 Postgraduate Research Associate  
Department of Immunology,  
The Institute of Medical Science,  
The University of Tokyo.  
Scientific Advisor: Professor Kiyoshi Takatsu
- 
- Research: Cellular mechanism of development of a retrovirus-  
induced immunodeficiency syndrome (MAIDS)
- 1991.4-1991.12 Postgraduate Research Associate  
Department of Biology,  
The Institute for Medical Immunology,  
Kumamoto University Medical School.  
Scientific Advisor: Professor Kiyoshi Takatsu  
Research: Signal transduction through IL-5 receptor and  
involvement of Xid defect in the receptor system.

## **Education:**

### **Medical School**

1981-1987 Kumamoto University Medical School

### **Graduate School**

1987-1991 Department of Biology,  
The Institute for Medical Science,  
Kumamoto University Medical School  
Research: Immunology  
Scientific Advisor: Professor Kiyoshi Takatsu

Thesis Dissertation: Role of interleukin 5 and its receptor in the immune system.

**Membership of learned societies:**

Japanese Society of Immunology

Japanese Cancer Association

**Honors and Fellowships**

Special Fellow of The Japanese Ministry of Education, Culture and Science,  
April 1990-March 1991.

The Uehara Memorial Foundation Fellowship, April 1995-March 1996.

## Publications

1. Mita, S., Harada, N., Naomi, S., **Hitoshi, Y.**, Sakamoto, K., Akagi, M., Tominaga, A. & Takatsu, K., (1988). Receptors for T cell-replacing factor / Interleukin 5 Specificity, quantitation, and its implication. *J. Exp. Med.*, 168, 863 - 878.
2. Jankovic, D.L., Abehsira-Amar, O., Korner, M., Roth, C., **Hitoshi, Y.**, Takatsu, K. & Theze, J., (1988). IL-4, but not IL-5, can act synergistically with B cell activating factor (BCAF) to induce proliferation of resting B cells. *Cell. Immunol.*, 117, 165 - 176.
3. **Hitoshi, Y.**, Mita, S., Tominaga, A., Kikuchi, Y., Sonoda, E., Takatsu, K. & Watanabe, Y., (1989). Interferon-gamma inhibits the proliferation but not the differentiation of murine B cells in response to IL-5. *Int. Immunol.*, 1, 185 - 190.
4. Tominaga, A., Mita, S., Kikuchi, Y., **Hitoshi, Y.**, Takatsu, K., Nishikawa, S.-I. & Ogawa, M., (1989). Establishment of IL-5-dependent early B cell lines by long-term bone marrow cultures. *Growth Factors*, 1, 135 - 146.
5. Matsumoto, R., Matsumoto, M., Mita, S., **Hitoshi, Y.**, Ando, M., Araki, S., Yamaguchi, N., Tominaga, A. & Takatsu, K., (1989). Interleukin-5 induces maturation but not class switching of surface IgA-positive B cells into IgA-secreting cells. *Immunology*, 66, 32 - 38.
6. Sonoda, E., Matsumoto, R., **Hitoshi, Y.**, Ishii, T., Sugimoto, M., Araki, S., Tominaga, A., Yamaguchi, N. & Takatsu, K., (1989). Transforming growth factor  $\beta$  induces IgA production and acts additively with interleukin 5 for IgA production. *J. Exp. Med.*, 170, 1415 - 1420.
7. Mita, S., Tominaga, A., **Hitoshi, Y.**, Sakamoto, K., Honjo, T., Akagi, M., Kikuchi, Y., Yamaguchi, N. & Takatsu, K., (1989). Characterization of high-affinity receptors for interleukin 5 on interleukin 5-dependent cell lines. *Proc. Natl. Acad. Sci. USA*, 86, 2311 - 2315.
8. Enokihara, H., Furusawa, S., Nakakubo, H., Kajitani, H., Nagashima, S., Saito, K., Shishido, H., **Hitoshi, Y.**, Takatsu, K., Noma, T., Shimizu, A. & Honjo, T., (1989). T cells from eosinophilic patient produce interleukin-5 with interleukin-2 stimulation. *Blood*, 73, 1809 - 1813.
9. Takaki, S., Tominaga, A., **Hitoshi, Y.**, Mita, S., Sonoda, E., Yamaguchi, N. & Takatsu, K., (1990). Molecular cloning and expression of the murine interleukin-5 receptor. *EMBO J.*, 9, 4367-4374.
10. Murata, Y., Yamaguchi, N., **Hitoshi, Y.**, Tominaga, A. & Takatsu, K., (1990). Interleukin 5 and interleukin 3 induce serine and tyrosine phosphorylation of several cellular proteins in an interleukin 5-dependent cell line. *Biochem. Biophys. Res. Commun.*, 173, 1102-1108.
11. Mita, S., Kikuchi, Y., **Hitoshi, Y.**, Sakamoto, K., Tominaga, A. & Takatsu, K., (1990). Cyclosporin A preferentially inhibits the differentiation of murine B cells in response to IL-5 and its restoration by IL-6. *Kumamoto Med. J.*, 42, 73-86.
12. **Hitoshi, Y.**, Yamaguchi, N., Mita, S., Sonoda, E., Takaki, S., Tominaga, A. & Takatsu, K., (1990). Distribution of IL-5 receptor-positive B cells : Expression of IL-5 receptor on Ly-1(CD5)<sup>+</sup> B cells. *J. Immunol.*, 144, 4218 - 4225.

13. Enokihara, H., Kajitani, H., Nagashima, S., Tsunogake, S., Takano, N., Saitou, K., Furusawa, S., Shishido, H., **Hitoshi, Y.** & Takatsu, K., (1990). Interleukin 5 activity in sera from patients with eosinophilia. *Brit. J. Haematol.*, 75, 458 - 462.
14. Yamaguchi, Y., Suda, T., Shiozaki, H., Miura, Y., **Hitoshi, Y.**, Tominaga, A., Takatsu, K. & Kasahara, T., (1990). Role of IL-5 in IL-2-induced eosinophilia In vivo and in vitro expression of IL-5 mRNA by IL-2. *J. Immunol.*, 145, 873 - 877.
15. Yamaguchi, N., **Hitoshi, Y.**, Mita, S., Hosoya, Y., Murata, Y., Kikuchi, Y., Tominaga, A. & Takatsu, K., (1990). Characterization of the murine interleukin 5 receptor by using a monoclonal antibody. *Int. Immunol.*, 2, 181 - 187.
16. Yamaguchi, Y., Suda, T., Suda, J., Eguchi, M., Miura, Y., Mita, S., **Hitoshi, Y.**, Tominaga, A. & Takatsu, K., (1990). Analysis of eosinophil-predominant colonies formed by human hemopoietic precursor cells in the presence of purified interleukin-5. *Acta Haematol. Jpn*, 53, 688 - 698.
17. Mita, S., Takaki, S., **Hitoshi, Y.**, Rolink, A.G., Tominaga, A., Yamaguchi, N. & Takatsu, K., (1991). Molecular characterization of the beta chain of the murine interleukin 5 receptor. *Int. Immunol*, 3, 665-672.
18. Tominaga, A., Takaki, S., Koyama, N., Katoh, S., Matsumoto, R., Migita, M., **Hitoshi, Y.**, Hosoya, Y., Yamauchi, S., Kanai, Y., Miyazaki, J.-I., Usuku, G., K-I, Y. & Takatsu, K., (1991). Transgenic mice expressing a B cell growth and differentiation factor gene (IL-5) develop eosinophilia and autoantibody production. *J. Exp. Med.*, 173, 429-437.
19. Yamaguchi, N., **Hitoshi, Y.**, Takaki, S., Murata, Y., Migita, M., Kamiya, T., Minowada, J., Tominaga, A. & Takatsu, K., (1991). Murine interleukin 5 receptor isolated by immunoaffinity chromatography: comparison of determined N-terminal sequence and deduced primary sequence from cDNA and implication of a role of the intracytoplasmic domain. *Int. Immunol.*, 3, 889-898.
20. **Hitoshi, Y.**, Yamaguchi, N., Korenaga, M., Mita, S., Tominaga, A. & Takatsu, K., (1991). In vivo administration of antibody to murine IL-5 receptor inhibits eosinophilia of IL-5 transgenic mice. *Int. Immunol.*, 3, 135-139.
21. Migita, M., Yamaguchi, N., Mita, S., Higuchi, S., **Hitoshi, Y.**, Yoshida, Y., Tomonaga, M., Matsuda, I., Tominaga, A. & Takatsu, K., (1991). Characterization of the human IL-5 receptors on eosinophils. *Cell. Immunol.*, 133, 484-497.
22. Korenaga, M., **Hitoshi, Y.**, Yamaguchi, N., Sato, Y., Takatsu, K. & Tada, I., (1991). The role of interleukin-5 in protective immunity to *Strongyloides venezuelensis* infection in mice. *Immunology*, 72, 502-507.
23. Sonoda, E., **Hitoshi, Y.**, Yamaguchi, N., Ishii, T., Tominaga, A., Araki, S. & Takatsu, K., (1992). Differential Regulation of IgA Production by TGF- $\beta$  and IL-5: TGF- $\beta$  induces Surface IgA-Positive Cells Bearing IL-5 Receptor, Whereas IL-5 Promotes Their Survival and Maturation into IgA-Secreting Cells. *Cell. Immunology*, 140, 158-172.

24. **Hitoshi, Y.**, Okada, Y., Sonoda, E., Tominaga, A., Makino, M., Suzuki, K., Kinoshita, J., Komuro, K., Mizuochi, T. & Takatsu, K., (1993). Delayed progression of a murine retrovirus-induced acquired immunodeficiency syndrome, MAIDS, in X-linked immunodeficient mice. *J. Exp. Med.*, 177, 621-626.
25. Katoh, S., Bending, M.M., Kanai, Y., Shultz, L.D., **Hitoshi, Y.**, Takatsu, K. & Tominaga, A., (1993). Maintenance of CD5+ B cells at an early developmental stage by interleukin-5 transgenic mice. *DNA AND CELL BIOLOGY*, 12, 481-491.
26. Nagai, H., Yamaguchi, S., Inagaki, N., Tsuruoka, N., **Hitoshi, Y.** & Takatsu, K., (1993). Effect of anti-IL-5 monoclonal antibody on allergic bronchial eosinophilia and airway hyperresponsiveness in mice. *Life sciences*, 53, 243-247.
27. **Hitoshi, Y.**, Sonoda, E., Kikuchi, Y., Yonehara, S., Nakauchi, H. & Takatsu, K., (1993). Interleukin 5 receptor positive B cells, but not eosinophils, are functionally and numerically influenced in the mice carrying the X-linked immune defect. *Int. Immunology*, 5, 1183-1190.
28. Fukuba, Y., Inaba, M., Taketani, S., **Hitoshi, Y.**, Adachi, Y., Tokunaga, R., Inaba, K., Takatsu, K. & Ikehara, S., (1994). Functional analysis of thymic B cells. *Immunobiol.*, 190, 150-163.
29. Miyake, K., Yamashita, Y., **Hitoshi, Y.**, Takatsu, K. & Kimoto, M., (1994). Murine B cell Proliferation and Protection from Apoptosis with an Antibody against a 105-kD Molecule: Unresponsiveness of X-linked Immunodeficient B Cells. *J. Exp. Med.*, 180, 1217-1224.
30. Sato, S., Katagiri, T., Takaki, S., Kikuchi, Y., **Hitoshi, Y.**, Yonehara, S., Tsukada, S., Kitamura, D., Watanabe, T., Witte, O. & Takatsu, K., (1994). IL-5 receptor-mediated tyrosine phosphorylation of SH2/SH3-containing proteins and activation of Bruton's tyrosine and Janus 2 kinases. *J. Exp. Med.*, 180, 2101-2111.
31. Uehara, S., **Hitoshi, Y.**, Numata, F., Makino, M., Howard, M., Mizuochi, T. & Takatsu, K., (1994). An IFN- $\gamma$ -dependent pathway plays a critical role in the pathogenesis of murine immunodeficiency syndrome induced by LP-BM5 MuLV murine leukemia virus. *Int. Immunol.*, 6, 1937-1947.
32. Korenaga, M., **Hitoshi, Y.**, Takatsu, K. & Tada, I., (1994). Regulatory effect of anti-interleukin 5 monoclonal antibody on intestinal worm burden in a primary infection with *Strongyloides Venezuelensis* in mice. *Int. J. Parasitology*, 24, 951-957.
33. Korenaga, M., **Hitoshi, Y.**, Takatsu, K. & Tada, I., (1995). Cross-resistance between *Strongyloides vebezuelensis* and *S. ratti* in mice. *J. Helminthology*, 69, 119-123.
34. Makino, M., Yoshimatsu, K., Azuma, M., Okada, Y., **Hitoshi, Y.**, Yagita, H., Takatsu, K., & Komuro, K., (1995). Rapid development of murine AIDS is dependent of signals provided by CD54 and CD11a. *J. Immunol.*, 155, 974-981.
35. Numata, F., **Hitoshi, Y.**, Uehara, S., & Takatsu, K. (1997). The xid mutation plays an important role in delayed development of murine acquired immunodeficiency syndrome. *Int. Immunol.*, 9, 139-46.

36. **Hitoshi, Y.**, Lorens, J. B., Kitada, S.-I., Fisher, J., LaBarge, M., Ring, H. Z., Francke, U., Reed, J. C., Kinoshita, S., & Nolan, G. P. (1998). Toso, a cell surface, specific regulator of Fas-induced apoptosis in T cells. *Immunity*, 8, 461-471
37. Rothenberg, M., Fisher, J., Zapol, D., Anderson, D., **Hitoshi, Y.**, Achacoso, P., and Nolan, G.P., (1998) Intracellular combinatorial chemistry with peptides in selection of Caspase-like inhibitors. NATO ASI Series, Vol. H 105:171-183. *Gene Therapy*.
38. Xu, X., Leo, C., Jang, Y., Chan, E., Padilla, D., Huang, B.C., Lin, T., Gururaja, T., **Hitoshi, Y.**, Lorens, J.B., Anderson, D.C., Sikic, B., Luo, Y., Payan, D.G., & Nolan, G.P. (2001). Dominant effector genetics in mammalian cells. *Nat. Genet.* 23-29
39. Kaspar, A.A., Okada, S., Kumar, J., Poulain, F.R., Drouvalakis, K.A., Kelekar, A., Hanson, D.A., Kluck, R.M., **Hitoshi, Y.**, Johnson, D.E., Froelich, C.J., Thompson, C.B., Newmeyer, D.D., Anel, A., Clayberger, C., & Krensky, A.M. (2001) A distinct pathway of cell-mediated apoptosis initiated by granulysin. *J Immunol.*, 167, 350-356.
40. Perez, O. D., Kinoshita, S., **Hitoshi, Y.**, Payan D. G., Kitamura T., Nolan, G. P., & Lorens J. B., (2002). Activation of the PKB/AKT pathway by ICAM2. *Immunity*, 1, 51-65

#### **Patent**

1. Toso, a cell-surface specific regulator of Fas-induced apoptosis in T cells  
Stanford Docket S98-019



## Exhibit 2

### Primers for TaHo Experiment

Forward primer	Reverse primer	Fluorescent probe
CGGATGATGTCAGCGCTCTT	CCTGGGCTTCTCACACCATT	CCCCATCTGCTCTGCCCTCTTG

### Thermal Cycle Conditions

Cycle	Temperature	Time	Repeat
Hold	50 C	2 min	
Hold	95 C	10 min	
Cycle	95 C	15 sec.	40 cycle
	60 C	1 min.	

Alignment of DNA sequences of 2.2412 (Tankyrse2 or TaHo) and Tankyrase by CLUSTAL W (1.8) multiple sequence alignment.

Sequences in bold and underline show sequence of 2.2412 forward primer.

\* indicates identify of sequence of 2.2412 (Tankyrase2) and Tankyrase.

```

Tankyrase2  -----
Tankyrase   ATGGCGGCGTCGCGTCGCTCTCAGCATCATCACCAACATCATCAACAACAGCTCCAGCCC

Tankyrase2  -----
Tankyrase   GCCCCAGGGGCTTCAGCGCCGCCGCCACCTCCTCCCCCACTCAGCCCTGGCCTGGCC

Tankyrase2  -----
Tankyrase   CCGGGGACCACCCCAGCCTCTCCACGGCCAGCGGCCTGGCCCCCTTCGCCTCCCCGCGG

Tankyrase2  -----
Tankyrase   CACGGCCTAGCGCTGCCGGAGGGGGATGGCAGTCGGGATCCGCCCCGACAGGCCCCGATCC

Tankyrase2  -----
Tankyrase   CCGGACCCGGTTGACGGTACCAGCTGTTGCAGTACCACCAGCACAATCTGTACCGTCGCC

Tankyrase2  -----
Tankyrase   GCCGCTCCCGTGGTCCCAGCGGTTTCTACTTCATCTGCCGCTGGGGTCGCTCCCAACCCA

Tankyrase2  -----
Tankyrase   GCCGGCAGTGGCAGTAACAATTCACCGTCGTCCTCTTCTTCCCCGACTTCTTCCTCATCT

Tankyrase2  -----ATGTCGG
Tankyrase   TCCTCTCCATCCTCCCCTGGATCGAGCTTGGCGGAGAGCCCCGAGGCGGCCGGAGTTAGC
                                           * * *

Tankyrase2  GTCGCCGCTGCGCCGGCGGG-GGAGCGGCCTGCGCGAGCGCCGCGGCCGAGGCCGTGGAG
Tankyrase   AGCACAGCACCCTGGGGCCTGGGGCAGCAGGACCTGGGACAGGGGTCCCAGCAGTGAGC
           * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Tankyrase2  CCGGCCGCCCGAGAGCTGTTGAGGCGTGCCGCAACGGGGACGTGGAACGAGTCAAGAGG
Tankyrase   GGGGCCCTACGGGAAGTGTGGAGGCTGTCGCAATGGGGACGTGTCCCGGGTAAAGAGG
           **** * * * * * * * * * * * * * * * * * * * * * * * *

```

Tankyrase2	CTGGTGACGCCTGAGAAGGTGAACAGCCGCGACACGGCGGGCAGGAAATCCACCCCGCTG
Tankyrase	CTGGTGACGCGGCAAACGTAAATGCAAAGGACATGGCCGGCCGGAAGTCTTCTCCCTG
	***** *
Tankyrase2	CACCTTCGCCGCGAGGTTTTGGGCGGAAAGACGTAGTTGAATATTTGCTTCAGAATGGTGCA
Tankyrase	CACCTTCGCTGCAGGTTTTGGAAGGAAGGATGTTGTAGAACACTTACTACAGATGGGTGCT
	***** *
Tankyrase2	AATGTCCAAGCACGTGATGATGGGGGCCCTTATTCCTCTTCATAATGCATGCTCTTTTGGT
Tankyrase	AATGTCCACGCTCGTGATGATGGAGGTCTCATCCCGCTTCATAATGCCTGTTCTTTTGGC
	***** *
Tankyrase2	CATGCTGAAGTAGTCAATCTCCTTTTGCGACATGGTGCAGACCCCAATGCTCGAGATAAT
Tankyrase	CATGCTGAGGTTGTGAGTCTGTTATTTGTGCCAAGGAGCTGATCCAAATGCCAGGGATAAC
	***** *
Tankyrase2	TGGAATTATACTCCTCTCCATGAAGCTGCAATTAAAGGAAAGATTGATGTTTGCATTGTG
Tankyrase	TGGAACATACACCTCTGCATGAAGCTGCTATTAAAGGGAAGATCGATGTGTGCATTGTG
	***** *
Tankyrase2	CTGTTACAGCATGGAGCTGAGCCAACCATCCGAAATACAGATGGAAGGACAGCATTGGAT
Tankyrase	CTGCTGCAGCACGGAGCTGACCCAAACATTCCGGAACACTGATGGGAAATCAGCCCTGGAC
	*** *
Tankyrase2	TTAGCAGATCCATCTGCCAAAGCAGTGCTTACTGGTGAATATAAGAAAGATGAACTCTTA
Tankyrase	CTGGCAGATCCTTCAGCAAAGCTGTCTTACAGGTGAATACAAGAAAGACGAACTCCTA
	* *
Tankyrase2	GAAAGTGCCAGGAGTGGCAATGAAGAAAAAATGATGGCTCTACTCACACCATTAAATGTC
Tankyrase	GAAGCTGCTAGGAGTGGTAATGAAGAAAACTAATGGCTTTACTGACTCCTCTAAATGTG
	*** *
Tankyrase2	AACTGCCACGCAAGTGATGGCAGAAAGTCAACTCCATTACATTTGGCAGCAGGATATAAC
Tankyrase	AATTGCCATGCAAGTGATGGGCGAAAGTCGACTCCTTTACATCTAGCAGCGGGCTACAAC
	* *
Tankyrase2	AGAGTAAAGATTGTACAGCTGTTACTGCAACATGGAGCTGATGTCCATGCTAAAGATAAA
Tankyrase	AGAGTTCGAATAGTTTCAGCTTCTTCTTCAGCATGGTGCTGATGTTTCATGCAAAAGACAAA
	***** *
Tankyrase2	GGTGATCTGGTACCATTACACAATGCCTGTTCTTATGGTCATTATGAAGTAACTGAACTT
Tankyrase	GGTGGACTTGTGCCTCTTCATAATGCATGTTTCATATGGACATTATGAAGTCACAGAAGT
	***** *
Tankyrase2	TTGGTCAAGCATGGTGCCTGTGTAAATGCAATGGACTTGTGGCAATTCCTCCTCTTCAT
Tankyrase	CTACTAAAGCATGGAGCTTGTGTTAATGCCATGGATCTCTGGCAGTTTACTCCACTGCAC
	* *
Tankyrase2	GAGGCAGCTTCTAAGAACAGGGTTGAAGTATGTTCTCTTCTCTTAAGTTATGGTGCAGAC
Tankyrase	GAGGCTGCTTCCAAGAACCGTGTAGAAGTCTGCTCTTTGTTACTTAGCCATGGCGCTGAT
	***** *

Tankyrase2	CCAACACTGCTCAATTGTCACAATAAAAGTGCTATAGACTTGGCTCCACACCACAGTTA
Tankyrase	CCTACGTTAGTCAACTGCCATGGCAAAAGTGCTGTGGATATGGCTCCAAC TCCGGAGCTT
	** ** * **** * ** ***** * ** ***** ** ** ** *
Tankyrase2	AAAGAAAGATTAGCATATGAATTTAAAGGCCACTCGTTGCTGCAAGCTGCACGAGAAGCT
Tankyrase	AGGGAGAGATTGACTTATGAATTTAAAGGTCATTCTTTACTACAAGCAGCCAGAGAAGCA
	* ** ***** * ***** ** ** ** ** ***** ** *****
Tankyrase2	GATGTTACTCGAATCAAAAAACATCTCTCTCTGGAAATGGTGAATTTCAAGCATCCTCAA
Tankyrase	GACTTAGCTAAAGTTAAAAAACACTCGCTCTGGAAATCATTAATTTCAAACAACCGCAG
	** * ** * * ***** ** ***** * ***** ** ** ** *
Tankyrase2	ACACATGAAACAGCATTGCATTGTGCTGCTGCATCTCCATATCCCAAAGAAAGCAAATA
Tankyrase	TCTCATGAAACAGCACTGCACTGTGCTGTGGCCTCTCTGCATCCCAAACGTAAACAAGTG
	* ***** ** ***** ** ***** ***** * ** ** *
Tankyrase2	TGTGAACTGTTGCTAAGAAAAGGAGCAAACATCAATGAAAAGACTAAAGAATTCTTGACT
Tankyrase	ACAGAATTGTTACTTAGAAAAGGAGCAAATGTTAATGAAAAAATAAAGATTTTCATGACT
	*** ***** ** ***** * ***** * ***** ** *****
Tankyrase2	CCTCTGCACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACAT
Tankyrase	CCCCTGCATGTTGCAGCCGAAAGAGCCCATAATGATGTCATGGAAGTTCTGCATAAGCAT
	** ***** ** ** * ** * ** ***** * ***** ** ** ** *
Tankyrase2	GAAGCAAAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATAT
Tankyrase	GGCGCCAAGATGAATGCACTGGACACCCTTGGTCAGACTGCTTTGCATAGAGCCGCCCTA
	* ** *** * ***** ** * ***** ** * ** ***** **
Tankyrase2	TGTGGTCATCTACAAACCTGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATA
Tankyrase	GCAGGCCACCTGCAGACCTGCCGCCTCCTGCTGAGTTACGGCTCTGACCCCTCCATCATC
	** ** ** * ***** ** ***** ** * ** ** * ** ** *
Tankyrase2	TCCCTTCAGGGCTTTACTGCTTTACAGATGGGAAATGAAAATGTACAGCAACTCCTCCAA
Tankyrase	TCCTTACAAGGCTTCACAGCAGCACAGATGGGCAATGAAGCAGTGCAGCAGATTCTGAGT
	*** * ** ***** ** ** ***** ***** ** ***** * **
Tankyrase2	GAGGGTATCTCATTAGGTAATTCAGAGGCAGACAGACAATTGCTGGAAGCTGCAAAGGCT
Tankyrase	GAGAGTACACCTATACGTACTTCTGATGTTGATTATCGACTCTTAGAGGCATCTAAAGCT
	*** *** * ** ***** ** * ** * * * * * ** ** *
Tankyrase2	GGAGATGTCGAAACTGTAAAAAACTGTGTACTGTTTCAGAGTGTCAACTGCAGAGACATT
Tankyrase	GGAGACTTGGAAGCTGTGAAGCAACTTTGCAGCTCTCAAATGTGAATTGTAGAGACTTA
	***** * ***** ** ***** ** * ***** * ** ***** *
Tankyrase2	GAAGGGCGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTG
Tankyrase	GAGGGCCGGCATTCCACGCCCTTACACTTCGCAGCAGGCTACAACCGCGTGTCTGTTGTA
	** ** ** * ** * ** * ** * ** ***** ** ** * ***** ** ** *
Tankyrase2	GAATATCTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCCTTGTAACCT
Tankyrase	GAGTACCTGCTACACCACGGTGCCGATGTCCATGCCAAAGACAAGGGTGGCTTGGTGCCC
	** ** ***** ** ** * ** ***** ***** ***** ** ** ***** ** ** *

Tankyrase2 TTGCACAATGCATGTTCTTATGGACATTATGAAGTTGCAGAACTTCTTGTTAAACATGGA  
 Tankyrase CTTCATAATGCCTGTTTCATATGGACACTATGAGGTGGCTGAGCTTTTAGTAAGGCATGGG  
 \* \* \* \* \*

Tankyrase2 GCAGTAGTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAA  
 Tankyrase GCTTCTGTCAATGTGGCGGACTTATGGAAATTTACCCCTCTCCATGAAGCAGCAGCTAAA  
 \* \* \* \* \*

Tankyrase2 GGAAATATGAAATTTGCAAACCTTCTGCTCCAGCATGGTGCAGACCCCTACAAAAAAAAC  
 Tankyrase GGAAAGTATGAAATCTGCAAGCTCCTTTTAAACATGGAGCAGATCCAATAAAAAGAAC  
 \* \* \* \* \*

Tankyrase2 AGGGATGGAAATACTCCTTTGGATCTTGTTAAAGATGGAGATACAGATATTCAAGATCTG  
 Tankyrase AGAGATGGAAATACACCTTTGGATTTGGTAAAGGAAGGAGACACAGATATTCAGGACTTA  
 \* \* \* \* \*

Tankyrase2 CTTAGGGGAGATGCAGCTTTGCTAGATGCTGCCAAGAAGGGTTGTTTAGCCAGAGTGAAG  
 Tankyrase CTGAAAGGGGATGCTGCTTTGTTGGATGCTGCCAAGAAGGGCTGCCTGGCAAGAGTGCAG  
 \* \* \* \* \*

Tankyrase2 AAGTTGTCTTCTCCTGATAATGTAAATTGCCGCGATACCCAAGGCAGACATTCAACACCT  
 Tankyrase AAGCTCTGTACCCAGAGAATATCAACTGCAGAGACACCCAGGGCAGAAATTCAACCCCT  
 \* \* \* \* \*

Tankyrase2 TTACATTTAGCAGCTGGTTATAATAATTTAGAAGTTGCAGAGTATTTGTTACAACACGGA  
 Tankyrase CTGCACCTGGCAGCAGGCTATAATAACCTGGAAGTAGCTGAATATCTTCTAGAGCATGGA  
 \* \* \* \* \*

Tankyrase2 GCTGATGTGAATGCCCAAGACAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTAC  
 Tankyrase GCTGATGTTAATGCCCAGGACAAGGGTGGTTTAATTCCTCTTACATAATGCGGCATCTTAT  
 \* \* \* \* \*

Tankyrase2 GGGCATGTAGATGTAGCAGCTCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGAC  
 Tankyrase GGGCATGTTGACATAGCGGCTTTATGATAAAATACAACACGTGTGTAAATGCAACAGAT  
 \* \* \* \* \*

Tankyrase2 AAATGGGCTTTCACACCTTTGCACGAAGCAGCCCCAAAAGGGACGAACACAGCTTTGTGCT  
 Tankyrase AAGTGGGCGTTTACTCCCTCCATGAAGCAGCCCAGAAAGGAAGGACGCAGCTGTGCGCC  
 \* \* \* \* \*

Tankyrase2 TTGTTGCTAGCCCATGGAGCTGACCCGACTCTTAAAAATCAGGAAGGACAAACACCTTTA  
 Tankyrase CTCCTCCTAGCGCATGGTGCAGACCCACCATGAAGAACCAGGAAGGCCAGACGCCTCTG  
 \* \* \* \* \*

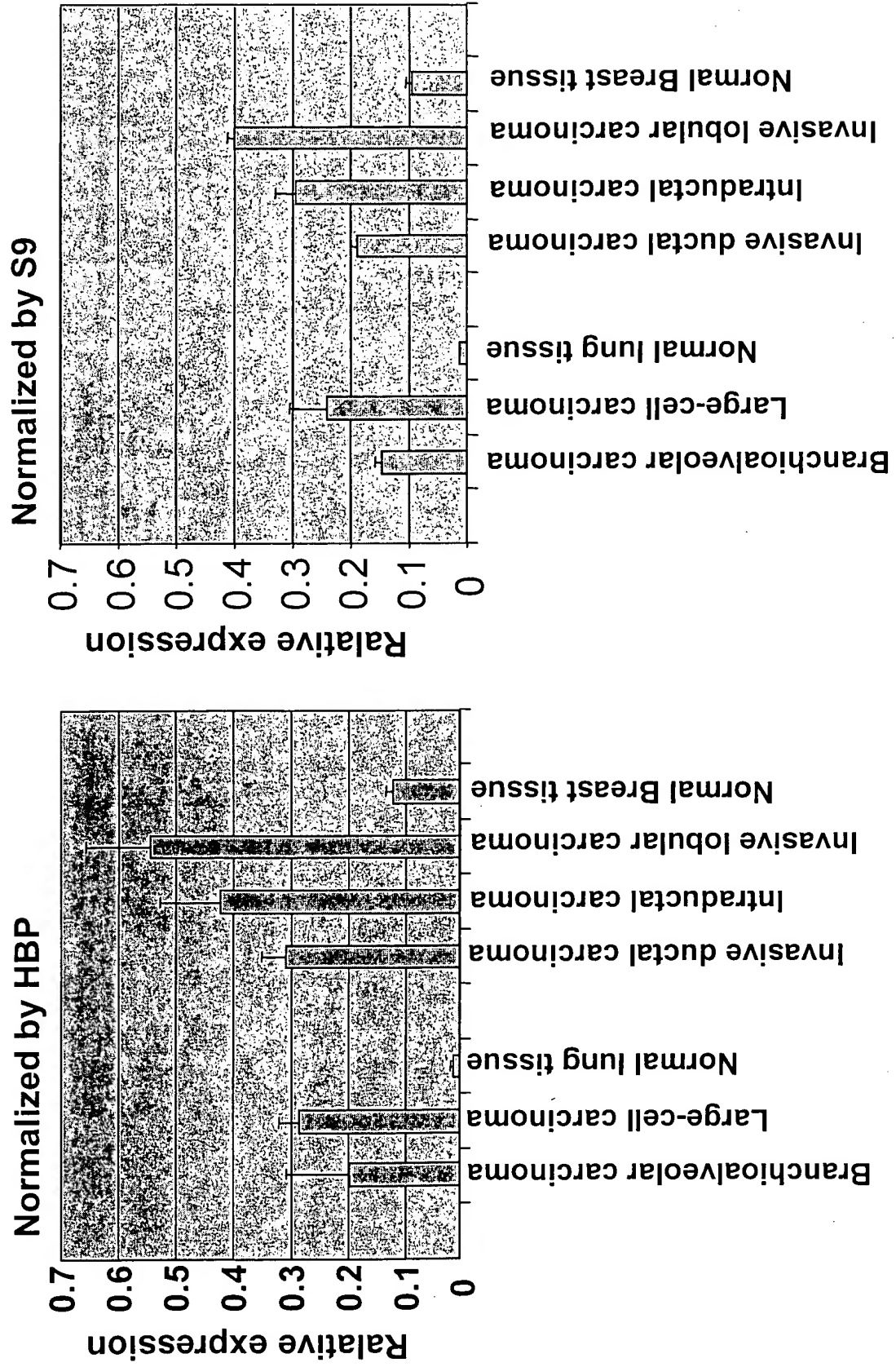
Tankyrase2 Forward Primer Fluorescent  
 GATTTAGTTTCAGCGGATGATGTCAGCGCTCTTCTGACAGCAGCCATGCCCATCTGCT  
 Tankyrase GATCTGGCAACAGCTGACGATATCAGAGCTTTGCTGATAGATGCCATGCCCCAGAGGCC  
 \* \* \* \* \*

probe Reverse primer  
 Tankyrase2 CTGCCCTCTTGTTACAAGCCTCAAGTGCTCAATGGTGTGAGAAGCCCAGGAGCCACTGCA  
 Tankyrase TTACCTACCTGTTTTAAACCTCAGGC--T-ACTGTAGTGAG---T----GCCTCTCTG  
 \* \* \* \* \*

Tankyrase2	GATGCTCTCTCTTCAGGTCCATCTAGCCCATCAAGCCTTTCTGCAGCCAGCAGTCTTGAC
Tankyrase	A-----TCTCACCAG---CATCCACCCCTCCTGCCTCTCGGCTGCCAGCAGCATAGAC **** * * * * * * * * * * * * * * *
Tankyrase2	AAC TTATCTGGGAG TTTTTCAGAACTGTCTTCAGTAGTTAGTTCAAGTGGAAACAGAGGGT
Tankyrase	AACCTCACTGGCCCTTTAGCAGAGTTGGCCGTAGGAGGAGCCTCCAATGCAGGGGATGGC *** * * * * * * * * * * * * * * *
Tankyrase2	GCTTCCAGTTTGGAGAAAAAGGAGGTTCAGGAGTAGATTTTAGCATAACT-----CAA
Tankyrase	GCCGCGGGAACAGAAAGGAAGGAAGGAGAAGTTGCTGGTCTTGACATGAATATCAGCCAA ** * * * * * * * * * * * * * * *
Tankyrase2	TTGTAAGGAATCTTGACTTGAGCACCTAATGGATATATTTGAGAGAGAACAGATCACT
Tankyrase	TTTCTAAAAAGCCTTGCCCTTGAACACCTTCGGGATATCTTTGAAACAGAACAGATTACA ** *** * * * * * * * * * * * * * * *
Tankyrase2	TTGGATGTATTAGTTGAGATGGGGCACAAGGAGCTGAAGGAGATTGGAATCAATGCTTAT
Tankyrase	CTAGATGTGTTGGCTGATATGGGTCTGAAGAGTTGAAAGAAATAGGCATCAATGCATAT * * * * * * * * * * * * * * * * * * *
Tankyrase2	GGACATAGGCACAACTAATTAAAGGAGTCGAGAGACTTATCTCCGACACAAGGTCTT
Tankyrase	GGGCACCGCCACAAATTAATCAAAGGAGTAGAAAGACTCTTAGGTGGACACAAGGCACC ** * * * * * * * * * * * * * * *
Tankyrase2	AACCCATATTTAACTTTGAACACCTCTGGTAGTGAACAATTCTTATAGATCTGTCTCCT
Tankyrase	AATCCTTATTTGACTTTTCACTGTGTTAATCAGGGAACGATTTTGCTGGATCTTGCTCCA ** * * * * * * * * * * * * * * *
Tankyrase2	GATGATAAAGAGTTTCAGTCTGTGGAGGAAGAGATGCAAAGTACAGTTCGAGAGCACAGA
Tankyrase	GAAGATAAAGAATATCAGTCAGTGAAGAAGAGATGCAAAGTACTATTCGAGAACACAGA ** * * * * * * * * * * * * * * *
Tankyrase2	GATGGAGGTCATGCAGGTGGAATCTTCAACAGATACAATATTTCTCAAGATTCAGAAGGTT
Tankyrase	GATGGTGGTAATGCTGGCGGCATCTTCAACAGATACAATGTCATTGCAATTCAAAAAGTT ***** * * * * * * * * * * * * * * *
Tankyrase2	TGTAACAAGAACTATGGGAAAGATACACTCACCGGAGAAAAGAAGTTTCTGAAGAAAAC
Tankyrase	GTCAACAAGAAGTTGAGGGAGCGGTTCTGCCACCGACAGAAGGAAGTGTCTGAGGAGAAT ***** * * * * * * * * * * * * * * *
Tankyrase2	CACAACCATGCCAATGAACGAATGCTATTTTCATGGGTCTCCTTTTGTGAATGCAATTATC
Tankyrase	CACAACCATCACAATGAGCGCATGTTGTTTCATGGTCTCCTTTTCATTAATGCCATTATT ***** * * * * * * * * * * * * * * *
Tankyrase2	CACAAAGGCTTTGATGAAAGGCATGCGTACATAGGTGGTATGTTTGGAGCTGGCATTAT
Tankyrase	CATAAAGGTTTGTGAGCGACATGCATACATAGGAGGAATGTTTGGGGCCGGGATTAT ** * * * * * * * * * * * * * * *
Tankyrase2	TTTGCTGAAAACCTCTTCCAAAAGCAATCAATATGTATATGGAATTGGAGGAGGTACTGGG
Tankyrase	TTTGCTGAAAACCTCCTCAAAAAGCAACCAATATGTTTATGGAATTGGAGGAGGAACAGGC ***** * * * * * * * * * * * * * * *

Tankyrase2	TGTCCAGTTCACAAAGACAGATCTTGTTACATTTGCCACAGGCAGCTGCTCTTTTGCCGG
Tankyrase	TGCCCCACACACAAGGACAGGTCATGCTATATATGTCACAGACAAATGCTCTTCTGTAGA
	** ** *
Tankyrase2	GTAACCTTGGGAAAGTCCTTTCCTGCAGTTCAGTGCAATGAAAATGGCACATTCTCCTCCA
Tankyrase	GTGACCCCTTGGGAAATCCCTTTCCTGCAGTTTAGCACCATGAAAATGGCCCACGCGCCTCCA
	** *
Tankyrase2	GGTCATCACTCAGTCACCTGGTAGGCCAGTGTAATGGCCTAGCATTAGCTGAATATGTT
Tankyrase	GGGCACCACCTCAGTCATTGGTAGACCGAGCGTCAATGGGCTGGCATATGCTGAATATGTC
	** ** *
Tankyrase2	ATTTACAGAGGAGAACAGGCTTATCCTGAGTATTTAATTACTTACCAGATTATGAGGCCT
Tankyrase	ATCTACAGAGGAGAACAGGCATACCCAGAGTATCTTATCACTTACCAGATCATGAAGCCA
	** *
Tankyrase2	GAAGGTATGGTCGATGG-ATAA-----
Tankyrase	GAAGCCCCCTTCCCAGACCGCAACAGCCGCAGAGCAGAAGACCTAG
	**** * * **

# Exhibit 3: Expression Analysis of 2.2412 (Tankyrase2/Tankyrase Homologue) by Taqman Assay



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